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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/709,801	05/28/2004	Caroline Desponts	USF-212XZ1T	2999

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EXAMINER	
ZARA, JANE J	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/709,801	DESPONTS ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *4-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/04,10/04,2/06,12/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 2-15-07.

Claims 1-18 are pending in the instant application.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-3, and newly added claim 18, and RNAi in hematopoietic stem cells, in the reply filed on 2-15-07 is acknowledged. The traversal is on the ground(s) that expanding the examination to include all cell types (e.g. not limited to hematopoietic stem cells) would not be burdensome to the examiner. Applicant's arguments are found persuasive, and the elected Group (see claim 3) has been examined as being drawn to all of the cell types listed.

The requirement is still deemed proper and is therefore made FINAL.

Claims 4-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2-15-07.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods of increasing the yield of stem cells in a patient, which stem cells comprise hematopoietic stem cells, mammary stem cells, mesenchymal and organ specific stem cells, which methods comprise administration of an RNAi compound that inhibits SHIP expression in a patient, harvesting stem cells from the patient, and optionally further comprising re-administering the harvested stem cells to the patient.

The specification and claims do not adequately describe the broad genus comprising RNAi compounds that provide for SHIP inhibition upon administration to a patient. The specification teaches the biochemical and immunological analyses of hematopoietic stem cells and early progenitor cells obtained from various SHIP mouse ablation models (see e.g. pages 13-23 of the specification, figures 1-13), as well as teaching the in vitro transfection of embryonic stem cells with two different SHIP-specific shRNA vectors, of undisclosed sequences (see p. 15 of the specification, and figure 4). The disclosure of in vitro inhibition of SHIP expression using two species (of undisclosed sequences) of shRNA molecules does not provide adequate written description for the broad genus of RNAi compounds claimed. The genus comprising RNAi compounds that inhibit SHIP expression in a patient potentially encompasses a

broad array of nucleic acid molecules. The instant disclosure and the art, however, fail to provide a representative number of species for the broad genus claimed. The specification and claims do not adequately describe the concise structural features (e.g. the nucleotide sequences) that distinguish structures within the genus from those without. No concise structural features or distinct characteristics have been disclosed in either the prior art or in the instant disclosure, which would allow one to discern between members of the genus from non-members. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the very broad genus claimed. Thus, Applicant was not in possession of the claimed genus, comprising any RNAi specific for SHIP-1 mRNA, and which, upon administration to a subject, inhibits SHIP expression in that subject that increases the yield of hematopoietic stem cells, mammary stem cells, mesenchymal and organ specific stem cells.

Claims 1-3 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro transfection of embryonic stem cells and subsequent inhibition of SHIP expression in vitro using two shRNA molecules of undisclosed sequences, and being enabling for the biochemical and immunological characterization of hematopoietic stem cells and early progenitor cells obtained from various SHIP mouse ablation models, does not reasonably provide enablement for methods of increasing the yield of stem cells in a patient, which stem cells comprise hematopoietic stem cells, mammary stem cells, mesenchymal and organ specific stem

cells, which methods comprise administration of any RNAi compound that inhibits SHIP expression in a patient, harvesting stem cells from the patient, and optionally further comprising re-administering the harvested stem cells to the patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods of increasing the yield of stem cells in a patient, which stem cells comprise hematopoietic stem cells, mammary stem cells, mesenchymal and organ specific stem cells, which methods comprise administration of any RNAi compound that inhibits SHIP expression in a patient, harvesting stem cells from the patient, and optionally further comprising re-administering the harvested stem cells to the patient.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of nucleic acid treatment in organisms. Branch teaches that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Cell culture examples are generally not predictive of in vivo inhibition of target genes (A. Branch, Trends in Biochem. Sci. 23: 45-50).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using oligonucleotide based approaches Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol., 14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: "It is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of ... oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic oligonucleotides to target cells).

See also the discussion by Opalinska et al of unpredictability of nucleic acid therapy, including the use of siRNA and antisense in vivo (Opalinska et al, Nature Rev., 1: 503-514, at 503 and 511). "Although conceptually elegant, the prospect of using nucleic-acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain... The main cause of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets. It is a widely held view that molecule delivery, and selection of which messenger RNA sequence to physically target, are core stumbling blocks that hold up progress in the field. ...it is widely appreciated that the ability of nucleic-acid molecules to modify gene expression in vivo is quite variable, and therefore wanting in terms of reliability." [references omitted].

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting the expression of SHIP-1 in vivo comprising the administration of any RNAi specific for SHIP mRNA. Applicants have not provided guidance toward a method of increasing the yield of stem cells in a patient upon administration of any RNAi. Applicants have shown an increase in stem and other progenitor cells in various mouse ablation models. Applicant has shown the inhibition of expression of SHIP in stem cells transfected in vitro with two different shRNA molecules of undisclosed sequences.

The ability to inhibit SHIP expression by in vitro transfection, and the observation of increased stem cell yields in SHIP mouse ablation models, however, are not

representative or correlative of the ability to increase the yield of hematopoietic stem cells, mammary stem cells, mesenchymal and organ specific stem cells in a patient comprising the administration by any route of any RNAi specific for SHIP mRNA. In addition, one skilled in the art would not accept on its face the examples given in the specification of in vitro transfections, or of biochemical, cellular and immunological characterization of stem and other progenitor cells obtained from mouse ablation models, as being correlative or representative of the ability to increase the yield of this wide array of stem cells in a subject in vivo using the large genus of interfering RNA specific for SHIP mRNA claimed and not adequately described, and further whereby stem cell yields are increased in a patient in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the efficacy of interfering RNA in inhibiting the expression of SHIP in any organism, whereby stem cell yields are increased. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and treatment effects provided by the claimed genus of RNAi compounds.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to compositions and methods of increasing the yield of stem cells in a patient, which stem cells comprise hematopoietic stem cells, mammary stem cells, mesenchymal and organ specific stem cells, which methods comprise administration of any RNAi compound that inhibits SHIP expression in a patient, harvesting stem cells from the patient, and optionally further comprising re-administering the harvested stem cells to the patient.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring the target gene or genes SHIP, whereby SHIP expression is inhibited in vivo, and further whereby hematopoietic stem cells, mammary stem cells, mesenchymal and organ specific stem cells have increased yields in a patient following the administration, by any means, of any RNAi of any size, specific for SHIP mRNA.

Since the specification fails to provide any particular guidance for the successful targeting and inhibition of expression of SHIPin vivo comprising administration of any nucleic acids encompassed by the broad genus claimed, or for the successful increase in yields of hematopoietic stem cells, mammary stem cells, mesenchymal and organ specific stem cells in a patient comprising administration of any RNAi compounds, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO

DUPLICATE CO PIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
3-15-07

JANE ZARA, PH.D.
PRIMARY EXAMINER